

Review Article

The Interplay Between Obesity and the Renin–Angiotensin System: Molecular Insights and Therapeutic Perspectives

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Abstract

Background and Aim: Obesity is a chronic multifactorial condition that is strongly associated with a wide range of cardiovascular and metabolic complications, including type 2 diabetes mellitus and metabolic syndrome. In addition to its well-established role in blood pressure regulation and electrolyte homeostasis, the renin–angiotensin system (RAS) has emerged as an important regulator of adipocyte biology, inflammatory signaling, oxidative stress, and systemic energy balance. In obesity, excessive activation of the RAS contributes to both metabolic and cardiovascular impairment, particularly through its effects on insulin resistance and chronic low-grade inflammation, supporting a reciprocal relationship between adiposity and RAS activity. This review summarizes current evidence on the obesity–RAS axis and evaluates the therapeutic potential of RAS-targeted strategies in obesity-related disorders.

Materials and Methods: A comprehensive review of the literature was undertaken to examine the role of RAS in obesity, with a particular focus on the interaction between the classical and counter-regulatory pathways, as well as the contribution of tissue-specific RAS to inflammation, insulin resistance, and metabolic dysfunction.

Results: Available evidence indicates that obesity is associated with increased angiotensin II production in adipose tissue, which promotes chronic inflammation, endothelial dysfunction, insulin resistance, and hypertension. Although central RAS activation may increase thermogenesis and reduce appetite, peripheral RAS activity appears to favor lipogenesis and metabolic deterioration. By contrast, the ACE2/angiotensin-(1–7)/Mas receptor axis exerts beneficial effects by improving vasodilatory capacity, enhancing insulin sensitivity and metabolic homeostasis, and attenuating oxidative stress and inflammatory responses. Consistent with these findings, pharmacological inhibition of the classical RAS, particularly with ACE inhibitors and angiotensin receptor blockers, has shown promising value in reducing obesity-associated metabolic and cardiovascular complications.

Conclusion: The relationship between obesity and the RAS is complex and bidirectional. Whereas activation of the classical RAS appears to drive disease progression, the counter-regulatory axis provides an important protective influence. Further studies are needed to refine RAS-based therapeutic strategies and to improve their clinical effectiveness in obesity-related metabolic disorders.

Keywords: Obesity, Renin–angiotensin system, Inflammation, Insulin resistance, Hypertension, Therapeutic strategies, Angiotensin II

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Introduction

Obesity is a major global health challenge and a leading driver of noncommunicable diseases worldwide (1). Its prevalence has increased substantially over recent decades, with more than 650 million adults currently living with obesity (1). Although obesity is commonly defined by a body mass index (BMI) of ≥ 30 kg/m², BMI remains an imperfect surrogate for adiposity because it does not fully reflect body composition or fat distribution (2,10,12). Nevertheless, it remains widely used due to its practicality and strong association with adverse metabolic and cardiovascular outcomes (10,13). Obesity is strongly associated with type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease (CVD), and several obesity-related cancers (2,3).

The pathophysiology of obesity is complex and involves interactions among genetic, metabolic, environmental, and behavioral factors (3,17,18). At the tissue level, excessive adipose expansion leads to adipocyte hypertrophy, adipokine dysregulation, ectopic lipid deposition, and chronic low-grade inflammation (5,6,24,25). These changes promote insulin resistance, oxidative stress, and progressive cardiometabolic dysfunction (24,32–36). Among the mechanisms implicated in obesity-related complications, dysregulation of the renin–angiotensin system (RAS) has gained increasing attention (4,5). Beyond its classical role in regulating blood pressure and fluid balance, the RAS also functions locally within adipose tissue, where it modulates inflammation, oxidative stress, vascular tone, and insulin signaling (5,8). Adipose tissue-derived RAS activity appears to contribute directly to obesity-associated hypertension and metabolic impairment (5,6).

Within the classical RAS pathway, angiotensin II (Ang II) is a major effector peptide that promotes adipocyte hypertrophy, endoplasmic reticulum stress, inflammatory signaling, and vascular dysfunction, thereby amplifying the harmful consequences of excess adiposity (4,7). In contrast, the counter-regulatory ACE2/angiotensin-(1–7)/Mas receptor axis exerts vasodilatory, anti-inflammatory, and

metabolically protective effects (8,9). An imbalance favoring the classical arm may therefore worsen obesity-related cardiovascular and metabolic injury, whereas enhancement of the protective axis may offer therapeutic benefit (8,9).

This review explores the bidirectional relationship between obesity and the RAS, focusing on the role of adipose tissue RAS dysregulation in metabolic and CVD and on the therapeutic potential of targeting this pathway in obesity-associated disorders.

Obesity

Definition, Epidemiology, and Pathophysiological

Consequences: In clinical practice and epidemiological research, adiposity is most commonly assessed using the BMI, calculated as body weight in kilograms divided by the square of height in meters (10). In adults, a BMI of 25.0–29.9 kg/m² is classified as overweight, whereas a BMI of 30.0 kg/m² or greater is classified as obesity. In children and adolescents aged 2–18 years, BMI should be interpreted using age- and sex-specific percentile charts to account for physiological variations in body composition during growth and development (11). Although BMI has recognized limitations, particularly its inability to fully reflect body fat distribution, body composition, and ethnic variation in adiposity, it remains a practical and widely used screening tool due to its strong epidemiological association with major obesity-related comorbidities, including T2DM, hypertension, and CVD (10,12). The risk of these complications generally increases with rising BMI and becomes more pronounced once BMI exceeds 30 kg/m², irrespective of sex (13).

Obesity is a chronic metabolic disorder characterized by adipocyte hypertrophy and hyperplasia, which lead to excessive expansion of adipose tissue (24). This pathologic expansion contributes to disease through 2 closely interconnected mechanisms: the mechanical burden imposed by excess fat mass and the endocrine dysfunction resulting from increased release of free fatty acids (FFAs) and bioactive adipokines (25). Together, these processes drive multisystem morbidity and promote the development of T2DM, CVD, osteoarthritis, and several obesity-associated malignancies (26). Beyond

these metabolic and structural consequences, obesity is also associated with substantial psychosocial burden, as weight stigma in educational, occupational, and healthcare environments may adversely affect mental health, particularly among women (27). In addition, obesity contributes to respiratory dysfunction, most notably obstructive sleep apnea (OSA), through pharyngeal fat deposition and reduced lung volumes (28). Cardiovascular adaptations to obesity include eccentric left ventricular hypertrophy secondary to chronic volume overload, increased cardiac output, and elevated wall stress, all of which increase the risk of arrhythmias and coronary heart disease (29). Furthermore, excessive weight gain may lead to dermatologic manifestations such as striae distensae, which arise from progressive stretching of the skin (30).

Obesity and Chronic Low-Grade Inflammation:

As these metabolic and endocrine abnormalities evolve, persistent low-grade inflammation becomes a key feature of the obese state. Expanded adipose tissue is no longer merely a storage site for excess energy but a biologically active tissue capable of sustaining inflammatory signaling (32,33). Hypertrophic adipocytes and infiltrating immune cells create a metabolically stressed microenvironment in which intracellular inflammatory pathways remain chronically activated. In particular, activation of c-Jun N-terminal kinase (JNK) and I κ B kinase (IKK) augments nuclear factor- κ B (NF- κ B) signaling and increases the expression of pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) (32). These mediators exacerbate adipose tissue dysfunction and interfere with insulin signaling, thereby contributing to systemic insulin resistance. In addition, activation of the NLRP3 inflammasome provides an important mechanistic link between adipose tissue stress and metabolic impairment by promoting the maturation and release of interleukin-1 β (IL-1 β) and interleukin-18 (IL-18) (33). Collectively, these processes place chronic inflammation at the center of obesity-related complications, particularly T2DM and CVD (32,33).

Obesity, T2DM, and Hypertension: Shared Pathophysiological Pathways: Obesity contributes to the development of T2DM through a complex interplay of insulin resistance, compensatory

hyperinsulinemia, and progressive pancreatic β -cell dysfunction. As adipose tissue expands, peripheral tissues become less responsive to insulin, prompting an initial increase in insulin secretion to maintain glucose homeostasis. Over time, however, this compensatory response becomes insufficient, and sustained β -cell stress may lead to functional decline and eventual exhaustion in susceptible individuals, resulting in persistent hyperglycemia (34,35). Visceral adiposity further disrupts metabolic homeostasis by increasing circulating FFAs, which interfere with glucose utilization through mechanisms such as the Randle cycle, impaired insulin signaling, and mitochondrial oxidative stress (36). In parallel, lipotoxicity amplifies insulin resistance and has been implicated in obesity-related hypertension through enhanced renal sodium retention and endothelial dysfunction (37). In addition, altered amino acid metabolism, particularly elevated levels of branched-chain amino acids, appears to support insulin secretion while simultaneously exacerbating insulin resistance, thereby contributing to the metabolic dysregulation characteristic of obesity (38).

These metabolic abnormalities are closely linked to obesity-related hypertension, in which renal injury and activation of the RAS play central roles. Obesity induces structural and functional changes in multiple organs, with the kidney being particularly vulnerable to the effects of excess adiposity (39,40). Visceral fat accumulation around the kidneys, together with increased intra-abdominal pressure, promotes sodium reabsorption and contributes to glomerular hyperfiltration, while obesity-associated vascular alterations further impair renal hemodynamics (41). In addition, visceral adipose tissue releases leptin and pro-inflammatory cytokines that exacerbate renal injury and amplify systemic hemodynamic stress (37). Dietary factors rich in lipids and carbohydrates increase circulating FFAs, which further disrupt vascular function by reducing nitric oxide bioavailability, increasing reactive oxygen species production, and impairing Na⁺/K⁺-ATPase activity (42). These changes, together with insulin resistance, chronic inflammation, and ectopic lipid deposition, intensify renal metabolic stress and accelerate structural deterioration of the kidney (40). At the same time, obesity promotes local angiotensinogen

production in adipose tissue and increases angiotensin II (Ang II) generation, thereby activating the RAS and facilitating vasoconstriction, sodium retention, and sympathetic overactivity(4,43). The resulting increase in vascular tone and α -adrenergic sensitivity creates a self-perpetuating cycle that sustains hypertension and links obesity to both renal dysfunction and cardiovascular risk (41).

Renin

Cellular Origin, Biosynthesis, and Regulatory Mechanisms in Physiological Homeostasis: Renin is a principal enzymatic component of the RAS and is predominantly synthesized and secreted by the juxtaglomerular cells of the kidney. By cleaving angiotensinogen to form angiotensin I (Ang I), renin initiates the cascade that ultimately leads to the generation of Ang II, a potent vasoactive peptide with a central role in the regulation of blood pressure and electrolyte balance (44). In addition to its established contribution to systemic hemodynamic control, renin-dependent RAS activity modulates renal perfusion, glomerular filtration, and several cellular processes, including growth and apoptosis (46). Through downstream Ang II signaling, this pathway also stimulates aldosterone secretion, thereby enhancing sodium and water reabsorption and helping maintain circulatory stability under physiological conditions (47).

The synthesis and release of renin are controlled by multiple regulatory mechanisms operating at different molecular levels. At the transcriptional level, renin gene expression is influenced by RNA polymerase II-dependent mechanisms and by steroid- and vitamin D-responsive regulatory elements (50). Post-transcriptional control further refines renin production through RNA-binding proteins that modulate messenger RNA stability and translation. In parallel, renin secretion is subject to intracellular signaling pathways, among which the so-called calcium paradox is particularly notable: increased intracellular calcium suppresses renin release, whereas cyclic AMP acts as a stimulatory signal (51). The integration of these transcriptional, post-transcriptional, and secretory mechanisms allows precise regulation of renin availability and supports physiological homeostasis.

Angiotensin Peptides: Structure, Function, and Regulatory Roles in the RAS Cascade:

Angiotensinogen is a 485-amino-acid glycoprotein of the serpin family and serves as the precursor molecule for the RAS, which plays a central role in regulating blood pressure, fluid balance, and cardiovascular homeostasis (5). The cascade is initiated when renin cleaves angiotensinogen to produce Ang I. Ang I is then converted to Ang II by angiotensin-converting enzyme (ACE), mainly in the pulmonary circulation, although this reaction also occurs in other tissues (5,62). As the major effector peptide of the system, Ang II exerts several important physiological effects. It causes vasoconstriction, increases systemic arterial pressure, enhances renal sodium reabsorption through the Na^+/H^+ exchanger, stimulates aldosterone secretion, and promotes both sympathetic activity and vasopressin release (64–66). Through these actions, Ang II contributes substantially to maintaining circulatory stability and body fluid homeostasis.

The role of the RAS is not limited to its classical endocrine pathway. Evidence from recent studies indicates that local RAS activity is present in several tissues, where it participates in regulating inflammation, tissue remodeling, and metabolic processes (56). In this context, angiotensinogen expression has also been demonstrated in extrahepatic sites, including the heart, brain, and adipose tissue, suggesting that it may act through local paracrine or autocrine mechanisms (58). These observations have increased interest in the contribution of tissue RAS to the development of metabolic and CVD. In addition, genetic variation in the angiotensinogen gene (AGT) has been associated with hypertension, further supporting the pathophysiological relevance of this pathway. (57,59).

The Non-Classical RAS

Counter-Regulatory Peptides and Their Physiological Implications:

The non-classical RAS includes several peptides that, in many settings, act antagonistically to Ang II and help maintain cardiovascular homeostasis. Among these, angiotensin-(1-7) [Ang-(1-7)] is among the best-characterized. It is generated primarily by angiotensin-converting enzyme 2 (ACE2) and exerts its effects via the Mas receptor. Experimental and clinical evidence

suggests that this peptide promotes nitric oxide-dependent vasodilation, reduces vascular inflammation, and attenuates fibrosis and hypertrophy in both cardiac and renal tissues (67,68–70). Because of these actions, Ang-(1-7) has been increasingly viewed as a protective mediator within the RAS and a potentially important target in conditions such as heart failure and metabolic syndrome (67,68–70).

Another peptide of interest in this counter-regulatory axis is angiotensin-(1-9) [Ang-(1-9)], which is produced from Ang I by ACE2(71). Available evidence indicates that Ang-(1-9) may oppose the effects of Ang II by limiting hypertension and cardiovascular remodeling, possibly through activation of the AT₂ receptor and inhibition of ACE (72). It has also been linked to enhanced bradykinin-mediated vasodilation, lower oxidative stress, and protection against cardiac hypertrophy (64). Taken together, these findings suggest that Ang-(1-9) may have a meaningful protective role in CVD and deserves consideration as a therapeutic target (71,73). Angiotensin A (Ang A) represents another alternative angiotensin peptide. It is formed by decarboxylation of the N-terminal aspartate residue of Ang II, which produces an alanine substitution at the first amino acid position (55,74). Although its structure differs only slightly from that of Ang II, its biological behavior is not identical. Ang A appears to have lower intrinsic activity at the AT₁ receptor and relatively greater selectivity for the AT₂ receptor (75,76). This may explain why its vasoconstrictor effect is weaker than that of Ang II and why it has been discussed as a possible counter-modulatory peptide in cardiovascular injury and hypertension (9,76).

Alamandine is a heptapeptide related structurally to Ang-(1-7) and is formed through decarboxylation, giving rise to Ala¹-Ang-(1-7) (77). In contrast to Ang-(1-7), which primarily signals through the Mas receptor, alamandine acts mainly via the Mas-related G protein-coupled receptor D (MrgD) (78,79). Studies in experimental models suggest that it exerts vasodilatory, anti-inflammatory, and antioxidant effects, and may also protect against cardiac and renal injury (79,80). Although this pathway remains less extensively characterized than other components

of the RAS, current evidence supports its relevance in cardiovascular and renal pathophysiology (79,80) (Table 1).

RAS and the Classical Pathway: The RAS is a key hormonal network that helps control blood pressure, fluid balance, and how blood vessels contract (44). We used to think of it simply as a straight line starting with renin, going through ACE and Ang II, and ending with aldosterone (44,81). While that basic path is still central, the whole picture is much wider. The system also relies on other signaling pathways, like those involving Ang-(1-7), alamandine, and the AT₂ receptor (82). On top of that, we now know that organs like the heart, kidneys, and fat tissue have their own local RAS setups. These local systems can drive hypertension and metabolic issues on their own, separate from what is happening in the general circulation (44,83). In the end, how the RAS behaves comes down to a balance between its classic vessel-constricting actions and these newer, protective pathways (62).

The classic side of the system starts in the kidneys. When blood flow to the kidneys drops, sodium levels at the macula densa fall, or beta₁-adrenergic receptors get activated, juxtaglomerular cells release renin into the bloodstream (84). Renin cuts angiotensinogen (which comes from the liver) to make angiotensin I (Ang I). From there, ACE clips Ang I to produce Ang II, the main driver of the pathway (5,85). Ang II then binds to the AT₁ receptor, which triggers blood vessel constriction, releases aldosterone, kicks the sympathetic nervous system into gear, and remodels blood vessels (55,62,86). If this loop stays turned on for too long, it leads to lasting high blood pressure and damages the heart and blood vessels over time (55,62,86).

Counter-Regulatory RAS Pathway

Pathophysiological Role and Therapeutic Implications: Cardiorenal homeostasis depends on the balance between the classical and counter-regulatory arms of the RAS (91). When the classical pathway is overactive, it promotes hypertension, inflammation, and organ damage. In contrast, the counter-regulatory axis helps protect the heart and kidneys by reducing these harmful effects (91).

The main components of this protective pathway are

Table 1. Key angiotensin peptides – types, structure, and functions.

Peptide	Structure	Formation Pathway	Receptors	Primary Functions	Clinical Relevance
Angiotensinogen	485-amino-acid glycoprotein (serpin)	Hepatic synthesis → cleaved by renin to Ang I	N/A	Precursor for Ang I; regulates RAS cascade.	AGT gene polymorphisms linked to hypertension. (57,59)
Angiotensin I (Ang I)	Decapeptide (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu)	Renin cleavage of angiotensinogen	N/A	Inactive intermediate for Ang II production.	Target for ACE inhibitors. (60)
Angiotensin II (Ang II)	Octapeptide (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe)	ACE-mediated cleavage of Ang I (or chymase)	AT1R, AT2R	- Vasoconstriction, hypertension. - Aldosterone release, Na ⁺ retention. - Pro-fibrotic, pro-inflammatory. - Vasodilation (NO release).	Implicated in hypertension, cardiac remodeling. AT1R blockers (e.g., losartan) used clinically. (62,66)
Angiotensin-(1-7) [Ang-(1-7)]	Heptapeptide (Asp-Arg-Val-Tyr-Ile-His-Pro)	ACE2-mediated degradation of Ang II	MasR	- Anti-inflammatory, anti-fibrotic. - Cardioprotective. - Vasodilation (bradykinin potentiation).	Therapeutic potential in heart failure, metabolic syndrome. (67,70)
Angiotensin-(1-9) [Ang-(1-9)]	Nonapeptide (Ang I minus C-terminal Leu)	ACE2 action on Ang I	AT2R	- Reduces oxidative stress, cardiac hypertrophy. - Weaker vasoconstriction than Ang II.	Emerging target for cardiovascular diseases. (71,73)
Angiotensin A (Ang A)	Ala ¹ -Ang II (decarboxylated Ang II)	Decarboxylation of Ang II	AT1R (weak), AT2R	- AT2R-mediated protective effects. - Vasodilation, anti-fibrotic.	Potential modulator of RAS in hypertension. (75,76)
Alamandine	Ala ¹ -Ang-(1-7)	Decarboxylation of Ang-(1-7)	MrgD	- Cardioprotective, renoprotective.	Novel therapeutic candidate for CVD and renal disease. (78,80)

ACE2, Ang-(1-7), and the Mas receptor (MasR). ACE2 is expressed in the heart, kidneys, lungs, and endothelium, where it converts Ang II into Ang-(1-7) and limits the vasoconstrictive and pro-fibrotic effects of the classical pathway (67,87,88). Ang-(1-7) then binds to MasR, leading to nitric oxide release, lower oxidative stress, vasodilation, and anti-inflammatory and anti-fibrotic effects (89,90). Other mediators, such as neutral endopeptidase (NEP) and the alamandine/MrgD axis, also contribute to this protective network (89,92).

Disturbance of this balance has been linked to hypertension, metabolic disorders, and heart failure (96). For this reason, restoring RAS balance has become an important therapeutic goal. Current treatments, including ACE inhibitors and ARBs, already improve cardiorenal outcomes by blocking

the classical pathway (85). More recent approaches aim to enhance the protective arm directly, using recombinant human ACE2, Ang-(1-7)-based therapies, and selective MasR or MrgD agonists. These strategies may offer new ways to reduce cardiovascular and renal injury (92) (Figure1).

Figure 1. Schematic representation of the dual-arm RAS and its functional equilibrium. This diagram illustrates the interplay between the system's detrimental and cytoprotective pathways. The classical cascade (shown in red) begins with the maturation of prorenin into renin, a step facilitated by enzymes such as cathepsin B. Subsequently, renin acts on angiotensinogen to yield Ang I, which is then converted to Ang II via ACE or through alternative pathways such as chymase. Signaling through the AT₁ receptor (AT₁R) by Ang II drives various pathological

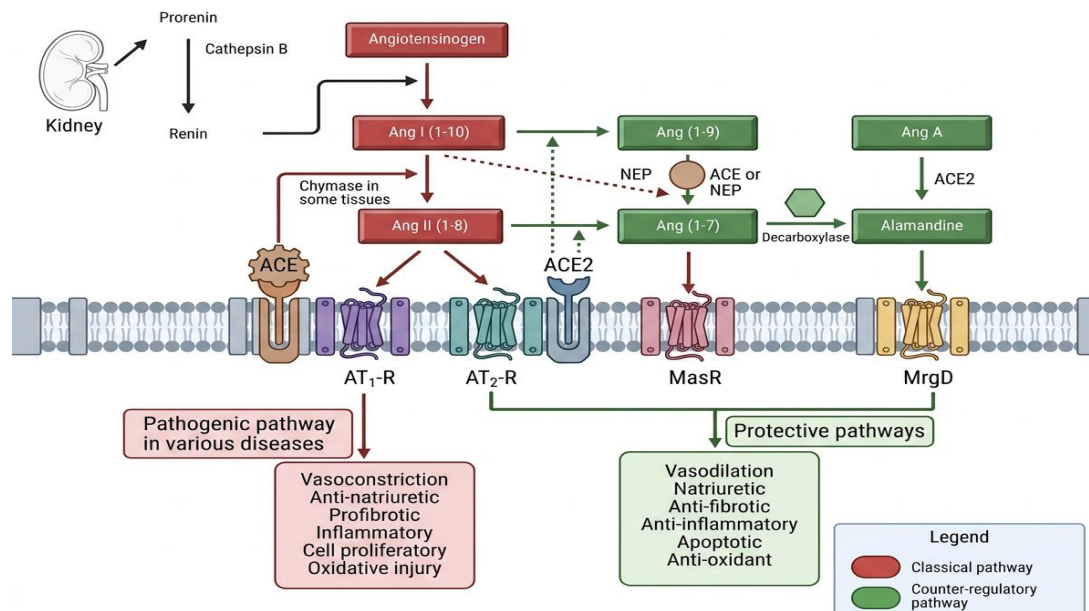


Figure 1. Overview of the *classical and counter-regulatory ras pathways*.

outcomes, including vasoconstriction, sodium conservation (anti-natriuresis), oxidative stress, and inflammatory responses. In contrast, the counter-regulatory axis (shown in green) functions as a physiological buffer. A key player here is ACE2, which hydrolyzes Ang II into Ang-(1-7). This peptide engages the MasR to trigger vasodilation, natriuresis, and anti-fibrotic signaling. Other protective elements include Ang-(1-9), derived from Ang I via NEP activity, and alamandine. Alamandine can be produced either via ACE2-mediated conversion of Ang A or via decarboxylation of Ang-(1-7), ultimately signaling through the MrgD receptor. Together, these interconnected pathways maintain a homeostatic balance, offering numerous targets for clinical modulation.

The Pathophysiological Link Between Tissue RAS Dysregulation and Inflammatory Processes: The tissue renin–angiotensin system (tRAS) acts as a local regulatory system that operates independently of the circulating RAS and plays an important role in regulating tissue-specific physiological and pathological processes. Through local production of angiotensin peptides, tRAS contributes to the regulation of cellular activity within individual organs. Notably, the generation of Ang II in tissues is

not limited to the classical ACE-dependent pathway, as enzymes such as chymase are also able to produce Ang II independently of ACE (44). Increasing evidence suggests that dysregulation of tRAS is involved in the development of several disorders, including hypertension, diabetic nephropathy, and obesity. In addition, overexpression of tRAS components has been observed in tissues such as the heart, kidneys, and adipose tissue (97). These findings highlight the importance of understanding how tRAS is regulated, since this may lead to the identification of more precise therapeutic approaches, particularly in conditions where systemic RAS inhibition alone does not provide sufficient protection (98).

The RAS is also closely linked to inflammatory processes, although its role is not entirely straightforward and appears to depend on the surrounding biological context (99). Among its components, Ang II is recognized as the main effector of the classical RAS pathway and is widely known for its predominantly pro-inflammatory actions, most of which are mediated through the AT₁R. Activation of this receptor promotes the release of pro-inflammatory cytokines and increases the expression of adhesion molecules, thereby enhancing the migration of immune cells into damaged tissues. These effects

contribute significantly to ongoing tissue injury and are considered key mechanisms in the progression of chronic kidney and CVD (55, 62).

In addition to stimulating inflammatory signaling, Ang II can suppress protective pathways. For example, it has been shown to reduce the expression of anti-inflammatory mediators, such as klotho and PGC-1 α , through both transcriptional and microRNA-mediated mechanisms (99). Ang II also influences adaptive immunity by shifting T-cell differentiation toward the Th17 phenotype, which is associated with stronger inflammatory responses, while simultaneously weakening beneficial immune regulation (100). Moreover, interaction between Ang II and TLR4 signaling may further amplify inflammation. Recent studies also indicate that Ang II may trigger regulated forms of cell death, including necroptosis, which can lead to the release of damage-associated molecular patterns (DAMPs), thereby intensifying inflammatory injury (101).

From a clinical perspective, inhibition of the RAS using ACE inhibitors or ARBs may help reduce inflammation-related tissue damage, especially in cardiovascular and renal disorders. This issue may be particularly relevant in obesity, a condition that is strongly associated with both hypertension and chronic low-grade inflammation. Therefore, improving our understanding of the interaction between obesity and RAS activity may offer valuable insight into new therapeutic strategies (102).

The Role of RAS Modulation in Obesity and Its Therapeutic Potential: Adipose tissue is increasingly recognized as an important extrarenal source of Ang II, as it expresses angiotensinogen and key components of the RAS, including ACE1 and ACE2 (4,103). In obesity, activation of the local adipose RAS contributes to a pro-inflammatory state and may also enhance aldosterone secretion through AT₁R stimulation, thereby influencing systemic metabolic and cardiovascular regulation (104). These effects may be partly attenuated by ACE inhibitors and AT₁R blockers, which have shown anti-inflammatory benefits in this setting (105). Adipose-derived Ang II also plays a role in obesity-related hypertension. It can increase sympathetic activity, stimulate renal renin release, and reinforce a cycle that further elevates Ang II and aldosterone levels

(106). In addition, it promotes vasoconstriction by reducing norepinephrine reuptake at vascular nerve endings (5). Although weight loss generally lowers blood pressure by reducing RAS overactivity (107), this effect may be partially limited by persistent adipokine-mediated sympathetic activation, including the influence of leptin (108). The effects of the RAS in obesity differ between its central and peripheral actions. Centrally, Ang II may reduce body weight by suppressing appetite and increasing thermogenesis in brown adipose tissue (109). In contrast, peripheral Ang II promotes lipogenesis, adipocyte hypertrophy, and insulin resistance, thereby aggravating obesity and metabolic dysfunction (58,110). Consistent with this, increased AGT expression in adipocytes has been linked to adipose tissue expansion (112).

These findings suggest that RAS modulation may offer therapeutic benefit in obesity. Inhibition of ACE or AT₁R can improve insulin sensitivity, reduce oxidative stress, limit adipocyte enlargement, and improve lipid and glucose metabolism (96,116). In addition, activation of the Ang-(1–7)/MasR and AT₂R pathways appears to promote energy expenditure and improve metabolic balance (118,119). Overall, targeting the RAS may represent a useful strategy for reducing the metabolic, inflammatory, and cardiovascular complications of obesity (5).

Conclusion

Overall, the evidence reviewed in this study shows that obesity is a complex and multifactorial disorder influenced by genetic background, environmental exposure, lifestyle behaviors, and metabolic alterations. Beyond its increasing global prevalence, obesity is closely linked to several important health problems, including hypertension, insulin resistance, CVD, and chronic low-grade inflammation. One of the major pathways involved in these complications appears to be the RAS, which has a broader role in obesity than was previously recognized.

Traditionally, the RAS has been described as a regulator of blood pressure and fluid balance. However, more recent findings suggest that it is also involved in adipose tissue biology, inflammatory processes, and metabolic regulation. In this context, adipose tissue is no longer viewed simply as a storage site for excess energy, but rather as an active

endocrine organ. By producing angiotensinogen and other components of the RAS, adipose tissue may contribute to both local and systemic RAS activation, particularly in obesity. This may, in turn, worsen metabolic disturbance and promote further tissue dysfunction.

An important finding across the studies reviewed is that RAS overactivation in obesity is mainly driven by the Ang II–AT₁R axis, which is associated with vasoconstriction, sodium retention, sympathetic stimulation, oxidative stress, and increased production of inflammatory cytokines such as IL-6, TNF- α , and IL-1 β . These changes not only support a persistent inflammatory state but also impair insulin signaling and contribute to the development of metabolic complications. In contrast, the ACE2/Ang-(1–7)/MasR pathway appears to exert protective effects by reducing inflammation, improving insulin sensitivity, and promoting vasodilation. This suggests that the clinical impact of RAS activity in obesity may depend largely on the balance between its harmful and protective pathways.

From a therapeutic perspective, these observations suggest that the RAS may be a meaningful target in the management of obesity-related disorders. ACE inhibitors and ARBs may be beneficial not only because they lower blood pressure, but also because they can reduce inflammatory activity, improve metabolic function, and protect against organ damage. In addition, newer approaches that enhance the protective arm of the RAS, such as ACE2 activation or MasR stimulation, may offer further benefit. Although more research is still needed to clarify their long-term value, these strategies may help provide a more integrated approach to obesity and its complications.

In summary, the relationship between obesity and the RAS is complex and bidirectional. A better understanding of this interaction may improve current therapeutic strategies and open new directions for the prevention and treatment of obesity-associated metabolic and cardiovascular complications.

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Conflict of interest

The authors further declare that, they have no conflict of interest.

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